C.3 Non-Technical abstract.

Multiple myeloma is a malignant disease with an increased number of cancerous plasma cells and an elevated monoclonal protein (“M-protein”) in the blood. Patients can have a mild course for several years. Indication of when to start treatment of active disease is marked by development of symptoms from the disease, such as elevated calcium levels, anemia, or bone lesions. If left untreated, most patients with active disease will die in 6 months. Standard chemotherapy will cause a complete disappearance of cancer in fewer than 5% of patients. The results from a large study showed that high-dose chemotherapy combined with infusion of the patient's own bone marrow cells ("autologous stem cell transplant") improved survival compared to standard dose chemotherapy alone. Based on this, chemotherapy followed by autologous stem cell transplant in subjects younger than 70 years with chemotherapy-sensitive disease is now the standard of care at most centers. Our proposal is a clinical trial in which tumor-specific vaccines will be added to the best standard of care just described. Vaccines will be given when the patient's tumors burden is relatively low which is when they hold the best promise of exerting an effective response.

The rationale for cancer vaccines is to cause a tumor-specific immune response in the patient. Cancer-cell vaccines genetically modified to secrete GM-CSF, a natural hormone that stimulates the immune system, have caused antitumor immunity in animal models of multiple different cancers. Additional animal studies have shown that GM-CSF does not need to be secreted directly from the tumor cell, but can be provided from a GM-CSF-secreting "Bystander" cell mixed with the tumor cells. Previous trials using GM-CSF-modified tumor vaccines in multiple cancer types have shown good safety profiles (predominantly redness, itching, and swelling at the vaccine site and flu-like symptoms) and evidence of immune and clinical antitumor responses.

The vaccine to be used in this study is composed of an irradiated human tumor cell line (K562) genetically modified to secrete GM-CSF, called K562 Bystander GVAX® or CG9962 that is mixed with autologous irradiated tumor cells. Both the tumor and Bystander cells are stored frozen prior to use. At the time of administration, the CG9962 cells and the tumor cells are thawed, mixed together to prepare the final vaccine (Myeloma Bystander GVAX®), and injected intradermally.

The proposed study is a Phase I/Il open-label clinical trial using the Myeloma Bystander GVAX vaccine after a bone marrow transplant for multiple myeloma. The vaccine will be administered at three dose levels. One vaccine will be administered before the bone marrow transplant. The posttransplant vaccinations will start 6 weeks after the transplant and will be administered every 3 weeks for a total of eight times.

Safety will be evaluated by standard laboratory blood tests, adverse events, and measurement in blood of autoimmune reactivity. Efficacy will be measured by monitoring patients for changes in tumor markers found in their blood, such as "M-protein," changes in tumor size, survival without further growth of the tumor, and overall survival. Immune reaction

evaluations will include determining how well the vaccine stimulates the immune system against multiple myeloma cancer cells in the body.

This phase I/Il study of Myeloma Bystander GVAX is currently ongoing. Enrollment has been completed and patient treatment and data analysis is in process. There are no plans to initiate any new trials with this vaccine product this year.